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08/982,272

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO
08/982,272	12/01/97	KIPPS	T 231/003

EXAMINER

HM12/0216

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ART UNIT	PAPER NUMBER
1644	22
1644	

DATE MAILED: 02/16/01

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 3/6/00; 8/3/00

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-86 is/are pending in the application.
Of the above, claim(s) 11-66, 68-82 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-10, 67, 83-86 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. The request filed 3/6/00 (Paper No. 17) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/982,272 is acceptable and a CPA has been established An Office Action on the CPA follows.

Applicant's election of the species (A) CD40 ligand alone as the accessory molecule ligand in Paper No. 21, filed 8/3/00, is acknowledged.

Claims 1-10, 67 and 83-86 are being acted upon as the elected invention.

Claims 11-66, 68-82 and the non-elected species have been withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to the nonelected inventions.

2. This Office Action will be in response to applicant's arguments, filed 3/6/00 (Paper No. 18). The rejections of record can be found in the previous Office Actions (Paper Nos. 9/14).

3. This application has been filed with informal drawings which are acceptable for examination purposes only.

4. Applicant's amendment, filed 7/19/99 (Paper No. 12), indicated that the various objections and informalities indicated in Paper No. 9 be held in abeyance pending notification of allowable subject matter.

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-10, 67 and 83-86 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is noted that this is a written description rejection under 35 U.S.C. 112, first paragraph

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are directed to "a member of the tumor necrosis factor family" . Such "members of the tumor necrosis factor family" do not meet the written description provision of 35 USC 112, first paragraph. There is insufficient guidance and direction as to the written description of the "member of the tumor necrosis factor family" intended and encompassed by the claimed methods.

In addition, the claims encompassing introducing a "gene" ; which encompass continuous or discontinuous regions encoding any member of the tumor necrosis family and may also contain additional coding and non-coding regions and, in turn, encompass the "gene".

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed "members of the tumor necrosis factor family" and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. For example the nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.
Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Therefore, there is insufficient written description for the "members of the tumor necrosis factor family" "CD40L "(elected species/invention), "Fas-ligand, CD70, TNFα, TNFβ, CD70, CD30 ligand, 41BB ligand, nerve growth factor and TRAIL".

Further,, applicants have not disclosed sufficient information which is 3' and 5' of the coding region of certain members of the tumor necrosis factor family; and, in turn, clearly lacks written description for the broad class of "genes" encompassed by the claimed methods..

7. Claims 1-10, 67 and 83-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "CD40L"(elected species/invention), "Fas-ligand, CD70, TNFα, TNFβ, CD70, CD30 ligand, 41BB ligand, nerve growth factor and TRAIL"; does not reasonably provide enablement for any "member of the tumor necrosis factor family". The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies "other members of the tumor necrosis factor family" other than those encompassed by CD40L"(elected species/invention), "Fas-ligand, CD70, TNFα, TNFβ, CD70, CD30 ligand, 41BB ligand, nerve growth factor and TRAIL". While "a member of the tumor necrosis factor family" may have some notion of the activity of the "accessory molecule ligand" to be used in the claimed methods; claiming biochemical molecules by a generic family name fails to distinctly enable any biochemical molecule that may be a member of the tumor necrosis factor family

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. a member of the tumor necrosis factor family; altering the immunoreactivity of human cells) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a limited number of structurally distinct molecules, albeit labeled generically as a member of the tumor necrosis factor family, and in turn utilizing predicted structural determinations to ascertain binding or functional aspects 'any member of the tumor necrosis factor family, including unknown members, and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

It has been known in the art that minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological or biological activities

The skilled artisan would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance based on in vitro characterization assays to direct a person of skill in the art to select particular sequences as essential for in vivo characterization of their ability to alter the immunoreactivity of human cells.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any "member of the tumor necrosis factor family" other than "CD40L"(elected species/invention), "Fas-ligand, CD70, TNFα, TNFβ, CD70, CD30 ligand, 41BB ligand, nerve growth factor and TRAIL".

8. Claims 1-10, 67 and 83-86 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the "partially derived accessory molecule ligand" that alters the immunoreactivity of human cells, encompassed by the claimed invention.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. partially derived accessory molecule ligand that alters the immunoreactivity of a human cell) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness.

However, the problem of predicting polypeptide structure from mere sequence data of a limited number of biochemical molecules and, in turn, utilizing predicted structural determinations to ascertain the ability of any partially derived elements of an accessory molecule ligand to alter immunoreactivity and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation.

In re Fisher, 166 USPQ 18 (CCPA 1970). indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. The relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of "partially derived accessory molecule ligands" with the ability to alter the immunoreactivity of human cells and have increased stability as well. Without sufficient guidance, the changes which can be made in the structure of "partially derived accessory molecule ligands" and still provide for increased stability and the ability to alter the immunoreactivity of human cells is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

9. Claims 1-10, 67 and 83-86 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-10, 67 and 83-86 are indefinite in its recitation of "altering the immunoreactivity" because it is ambiguous as to the direction (positive or negative) or degree of said "altering". The term "altering" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention

B) Claims 1-10, 67 and 83-86 are indefinite in its recitation of "increased stability" because this "phrase"" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention

C) Claim 85 is objected to because "TNFα" is recited twice as a member of the Markush.

D) Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Applicant's amended claims, filed 3/6/00 (Paper no. 18) have obviated the previous rejection under 35 U.S.C. § 102(e) as being anticipated by Freeman et al. (U.S. Patent No. 5,861,310)

13. Claims 1-8, 10 and 83 are rejected under 35 U.S.C. § 102(b) as being anticipated by Yellin et al. (J. Immunol., 1994) for the reasons of record set forth in Paper Nos. 9/14.

Applicant's arguments, filed 3/6/00 (Paper No. 10), have been fully considered but are not found convincing essentially for the reasons of record set forth in Paper Nos. 9/14. Applicant continues to argue that fails to note any mention of tranfection in this reference and that the limitation of increased stability of the accessory molecule on the surface of the cells is not disclosed. Applicant asserts that the CD40L transfected cells in the reference do not become immunostimulated.

However as pointed out previously; this reference relies upon the T-BAM/CD40L expressing or transfected D1.1 cell line (as well as the B2.7 clone) (see Materials and Methods, Cell Lines).

Comparison of methods of making the CD40L transfected cells with prior art is difficult since the Office is not equipped to manufacture the claimed products.

It appears that the claimed methods and the referenced methods employ the same ingredients and method steps.

Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Therefore, the claimed methods of making CD40L transfected cells are met by the prior art.

It is noted that applicant's reliance on of the immunostimulation of the transfected cells is not a limitation of the claimed methods. By making CD40L transfected cells, the ordinary artisan has altered the immunoreactivity of said cells by transfecting them with the costimulatory molecule CD40L.

Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999) for the inherency of methods.

Therefore, this reference teaches altering the immunoreactivity of human cells encoding the accessory molecule ligand CD40L.

Applicant's arguments are not found persuasive.

14. Claims 1-10, 67 and 83 are rejected under 35 U.S.C. § 102(e) as being anticipated by Spriggs et al. (U.S. Patent No. 6,016,832). Spriggs et al. teach transfecting human cells, including hemopoietic cells, lymphoid cells (column 7, paragraph 2), T cells (column 6, paragraph 3) and embryonic stem cells (column 7, paragraph 4), with CD40L and modifications thereof for treatment (as well as various uses in models such as testing vaccine preparation column 7, paragraph 5) (see entire document, including Summary of the Invention, Detailed Description of the Invention,). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods.

15. Claims 1-10, 67 and 83 are rejected under 35 U.S.C. § 102(e) as being anticipated by Maraskovsky et al. (U.S. Patent No. 6,017,572). Maraskovsky et al. teach transfecting human dendritic cells with CD40L and modifications thereof to augment responses to desired antigens (see entire document, including Summary of the Invention, Detailed Description of the Invention,). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods.

16. Claims 1-10, 67 and 83 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Freeman et al. (U.S. Patent No. 5,861,310) in view of Yellin et al. (J. Immunol., 1994) and Alderson et al. (J. Exp. Med., 1993) as well as pages 40-53 of the instant specification for the reasons of record set forth in Paper Nos. 9/14
AND/OR
Spriggs et al. (U.S. Patent No. 6,016,832) AND/OR
Maraskovsky et al. (U.S. Patent No. 6,017,572).

Applicant's amendment, filed 3/6/00 (Paper No. 18), have been fully considered but are not found convincing essentially for the reasons of record set forth in Paper Nos. 9/14.

Applicant argues that the reference teach transection of cells with genes that encode accessory molecules that are characteristics of those very cell types; while applicant's inventions is different in that it teaches the useful tranfection of accessory molecule ligand genes that are not functionally expressed in cells which express the corresponding and complementary accessory molecules.

Applicant is arguing limitations not claimed.

Given the lack of additional arguments addressing this rejection under 35 U.S.C. § 103(a) other than the reliance on addressing these references as they apply in the rejection under under 35 U.S.C. § 102; the previous obviousness rejection is maintained and reiterated herein for applicant's convenience.

The instant claims are drawn to methods of altering the immunoreactivity of human cells or treating human neoplasia by inserting CD40L

Freeman et al. teach altering the reactivity of a cell and treating human neoplasia by introducing a gene encoding an accessory molecule ligand (B7) alone or together, that is to be expressed on a cell surface, including tumor cells (see entire document). Freeman et al. differs from the instant elected invention by not disclosing CD40 ligand as a costimulatory or accessory molecule

Yellin et al. teach that transfecting cells, including leukemia cells, with CD40 ligand enhances a cell costimulatory activity, including the priming and clonal expansion of antigen specific T cells as well as providing helper function for cytotoxic T cell responses (see entire document, including the Abstract and Discussion).

Alderson et al. teach that CD40 ligand transfected cells induce monocytes to become tumoricidal against human melanoma cells, which indicated that the CD40 ligand had potent biological effects (see entire document, including the Abstract and Discussion). Alderson et al. teach transection with either murine or human CD40 ligand (for example, see page 671).

Therefore, it would have been prima obvious to the ordinary artisan at the time the invention was made to substitute the potent costimulatory/accessory molecule properties of the CD40 ligand into the methods of Freeman et al. to alter the immunoreactivity of cells, that is, to increase antigen presentation and/or immunoreactivity. The claimed limitations encompassing chimeric genes and vectors were known and practiced by the ordinary artisan at the time the invention was made, as evidenced by Freeman et al. Pages 40-53 of the instant specification also acknowledges that the general methods of providing chimeric/gene therapy constructs as well as manipulating cells for were known and practiced at the time the invention was made.

Spriggs et al. (U.S. Patent No. 6,016,832) and Maraskovsky et al. (U.S. Patent No. 6,017,572) have been added as additional teachings of transfecting various human cell types with CD40L and modifications of said CD4OL to provide the biological activity of CD40L in order to stimulate immune responses (see entire document, including Sections indicated above).

One of ordinary skill in the art at the time the invention was made would have been motivated to select CD40 ligand as an accessory molecule ligand to express in cells, including tumor cells, to increase their immunoreactivity. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
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